PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference -880-	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/IL2004/000507	International filing date *(day/month/year)* 13.06.2004	Priority date *(day/month/year)* 12.06.2003

International Patent Classification (IPC) or national classification and IPC
C12N6/06, A61K35/12, A61K38/17, A61K35/30, C12N5/06

Applicant
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1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
03.01.2005	30.06.2005

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

10/560294
International application No.
PCT/IL2004/000507

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-45 as originally filed

Claims, Numbers

1-53 as originally filed

Drawings, Sheets

1/2-2/2 as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 37-53 with respect to industrial applicability

because:

☒ the said international application, or the said claims Nos. 37-53 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-9, 11-53
	No:	Claims	10
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-9, 11-53
Industrial applicability (IA)	Yes:	Claims	1-36
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Present application relates to the use of gp130 activators, in particular IL6R/IL6 chimera to promote the formation of oligodendrocytes (ODC) from embryonic stem cells (ES), embryoid bodies (EB) and/or neurosphere (NS) cells. Methods for generating ODCs as well as use of said ODCs in the manufacture of a medicament for the treatment of neurodegenerative diseases or posttraumatic nerve damage are claimed. Said application further claims pharmaceutical compositions comprising ES, EB and/or NS cells and gp130 activators selected from CNTF, OSM, IL6 , IL6R/IL6 chimera and IL-11.

Re Item II

Priority

II.1 The International Preliminary Examination Report has been based on an assumed valid priority for the present application. Should the priority of the present application not be valid, the P,X document cited in the Search Report would be relevant with respect to novelty and inventive step (Article 33(2) and 33(3) PCT).

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

III.1 Claims 37 - 53 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.1 The following documents were taken into account:

D1: VALERIO A ET AL: "A SOLUBLE INTERLEUKIN-6 (IL-6) RECEPTOR/IL-6 FUSION PROTEIN ENHANCES THE IN VITRO DIFFERENTIATION OF RAT OLIGODENDROCYTES" ABSTRACTS OF THE SOCIETY FOR NEUROSCIENCE, SOCIETY FOR NEUROSCIENCE, WASHINGTON, DC, US, vol. 27, no. 2, 2001, page 2381, XP001146998 ISSN: 0190-5295

D2: BRÜSTLE O ET AL: "Embryonic stem cell-derived glial precursors: a source

of myelinating transplants." SCIENCE. 30 JUL 1999, vol. 285, no. 5428, 30 July 1999 (1999-07-30), pages 754-756, XP002292501 ISSN: 0036-8075

D3: BILLON NATHALIE ET AL: "Normal timing of oligodendrocyte development from genetically engineered, lineage-selectable mouse ES cells." JOURNAL OF CELL SCIENCE. 15 SEP 2002, vol. 115, no. Pt 18, 15 September 2002 (2002-09-15), pages 3657-3665, XP002292503 ISSN: 0021-9533

D4: WO 00/78331 A (BOSCHERT URSULA ; CHEBATH JUDITH (IL); REVEL MICHEL (IL); YEDA RES & D) 28 December 2000 (2000-12-28)

D5: GAGE F H: "Mammalian neural stem cells." SCIENCE. 25 FEB 2000, vol. 287, no. 5457, 25 February 2000 (2000-02-25), pages 1433-1438, XP002292502 ISSN: 0036-8075

V.2 Claim 10 is a so-called "product-by-process" claim. In the present case the term "obtainable" is to be interpreted in the way that the claimed ODCs can be **optionally** obtained by a method according to claims 1 - 9. Thus, since ODCs are well known in the prior art and moreover, since ODCs that are "obtainable" by the methods according to claims 1 - 9 are not distinguishable from ODCs disclosed in the prior art (see e.g. D1: Abstract, Figure 1; D3: Figure 4 and 5) the subject-matter referred to in claim 10 appears not to be novel under Article 33(2) PCT. The Applicant is further reminded that no unified criteria exist among the PCT member states for the assessment of such claims. The EPO, for example considers that "product-by-process" claims are only admissible if the products as such fulfill the requirements for patentability, i.e. inter alia they are novel and inventive and there is no other information available which could enable the Applicant to define the product satisfactorily by reference to its composition, structure or some other testable parameter.

V.3 Document D1, which is considered to represent the most relevant state of the art to the subject matter of claim 1, discloses that IL6R/IL6 chimera strongly enhance the differentiation of rat oligodendrocyte progenitor cells (OPCs) into highly arborized, mature ODC and that said IL6R/IL6 chimera also sustain their survival. The Authors further show that as OPCs differentiate they express the major myelin glycolipid GalC and that continued maturation results in elevated expression of major myelin proteins such as MBP and proteolipid protein (Abstract; Figure 4; page 607, column 2, paragraph 3 - page 610, column 1, paragraph 1; page 610, column 2, paragraph 3 - page 611, column 1, paragraph

2).

The subject-matter of independent claim 1 differs from the disclosure of D1 in that the starting cells that were used in order to generate ODCs are ES cells and not OPCs.

The problem to be solved by the present invention may therefore be regarded as the provision of an alternative method/way for the generation of ODCs.

In view of D2 the solution proposed in claim 1 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons: D2 already discloses that ES cells can be used for the generation of precursors for oligodendrocytes (page 754, column 1, paragraph 3 - column 2, paragraph 1; Figure 1A). The precursor cells disclosed in D2 as well as the OPCs described in D1 are both characterised by a positive staining with the monoclonal antibody A2B5 (D1: page 611, column 2, paragraph 2).
Therefore the features disclosed in D1 and D2 would be combined by the skilled person, without exercise of any inventive skills in order to solve the problem posed. The proposed solution in independent claim 1 as well as in the dependent claims 2 and 3 thus cannot be considered inventive (Article 33(3) PCT).
Same applies for the subject-matter referred to in claims 30 - 32.

V.4 Claims 4 - 6 that refer to the use of EB and/or NS cells are not considered to be inventive, since it is of general knowledge that these cells are directly derived from ES cells and that it would be straightforward and with reasonable expectation of success to use these cells for the generation of OPCs, respectively ODCs (see also D3: Figure 1 and D5). Hence, said claims appear to lack inventive step (Article 33(3) PCT). Same applies for the subject-matter referred to in claims 7 and 8.

V.5 Claim 9 appears not to fulfill the requirements of Article 33(3) PCT, since it only specifies some well known demyelinating diseases.

V.6 In view of the cited prior art that also suggests that the ODCs are used as cell transplants for myelin diseases (e.g. D3: Abstract; D2: Abstract, page 756, column 1, last paragraph), the subject-matter referred to in claim 11 appears not ot be inventive under Article 33(3) PCT.

V.7 Dependent claims 12 - 29 and 33 - 53 do not appear to contain any additional features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT with respect to inventive step, the reasons (see also comments under points V.3 - V.6).

V.8 For the assessment of the present claims 37 - 53 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observations on the international application

1) In their present wording, claims 1 - 53 embrace ***human embryonic stem cells****. Should the Applicant consider entering the European Regional Phase by precaution he is informed that said claims comprise subject matter that under the EPC is considered to be contrary to morality and is therefore not allowable.*

2) Claim 30 - 36 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved (...."suitable for..."), which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.

3)The terms "mutein, functional derivative, active fraction, circularly permutated derivative" used in claims 2, 13, 23, 31, and 41 are vague and unclear and leave the reader in doubt as to the meaning of the technical features to which they refer, thereby rendering the definition of the subject-matter of said claims unclear, Article 6 PCT.